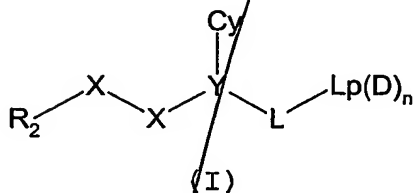


## Claims

1. A serine protease inhibitor compound of formula (I)



wherein:

$R_2$  is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,  $\text{MeSO}_2$ - or  $R_1$ , or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or  $R_{1j}$ , and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that  $R_2$  cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO,  $\text{CR}_{1a}$ ,  $\text{C(R}_{1a})_2$  or  $\text{NR}_{1a}$  group, at least one X being C, CO,  $\text{CR}_{1a}$  or  $\text{C(R}_{1a})_2$ ;

each  $R_{1a}$  independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$R_1$  is as defined for  $R_{1a}$ , provided that  $R_1$  is not unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a  $CR_{1b}$  group;

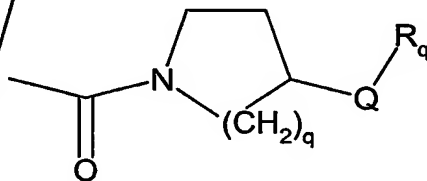
Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups  $R_{3a}$  or  $R_{3i}X_i$ ;

5 each  $R_{3a}$  independently is  $R_{1c}$ , amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a  
10 group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S; and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or  $-OCH_2O-$  which is bonded to two adjacent  
15 ring atoms in Cy;

$X_i$  is a bond, O, NH or  $CH_2$ ;

$R_{3i}$  is phenyl, pyridyl or pyrimidinyl optionally substituted by  $R_{3a}$ ; and

$R_{1b}$ ,  $R_{1c}$  and  $R_{1j}$  are as defined for  $R_{1a}$ ,  
20 and  $-L-Lp(D)_n$  is of the formula:



wherein:

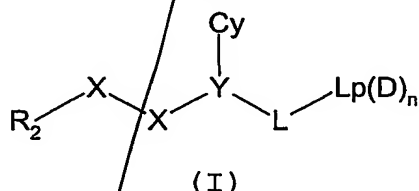
$q$  is 1 or 2;

$Q$  is  $-O-$  or  $-NH-$ ;

25 and  $R_q$  is  $R_c$  which is pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl or phenyl (which phenyl or pyridyl group may bear a fluoro, chloro, alkyl,  $CONH_2$ ,  $SO_2NH_2$ , dialkylaminosulphonyl, methoxy, methylthio, alkylsulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino,  
30 alkoxycarbonyl, acetylamino, cyano, ethoxy, nitro, hydroxy,

alkylsulphonylamino, triazolyl or tetrazolyl substituent);  
or a physiologically-tolerable salt thereof.

2. A serine protease inhibitor compound of formula (I)



wherein:

$R_2$  is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,  $\text{MeSO}_2^-$  or  $R_1$ , or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or  $R_{1j}$ , and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that  $R_2$  cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO,  $\text{CR}_{1a}$ ,  $\text{C(R}_{1a})_2$  or  $\text{NR}_{1a}$  group, at least one X being C, CO,  $\text{CR}_{1a}$  or  $\text{C(R}_{1a})_2$ ;

each  $R_{1a}$  independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

$R_1$  is as defined for  $R_{1a}$ , provided that  $R_1$  is not

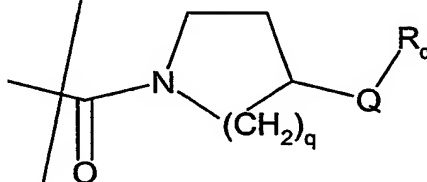
unsubstituted aminoalkyl;

Y (the  $\alpha$ -atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R<sub>3a</sub> or phenyl optionally substituted by R<sub>3a</sub>;

each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>, and -L-Lp(D)<sub>n</sub> is of the formula:



wherein:

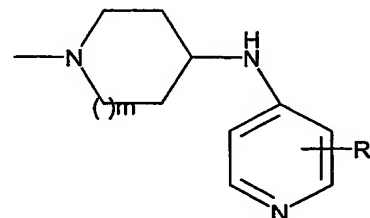
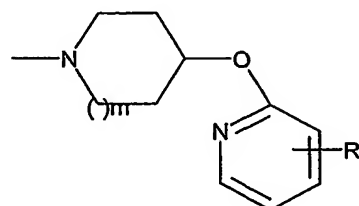
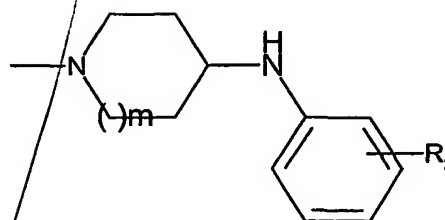
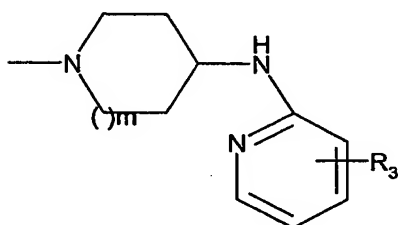
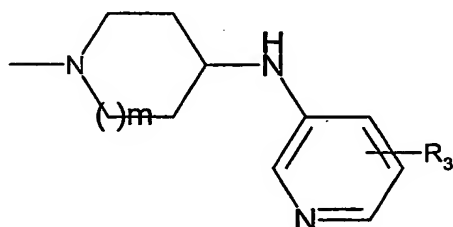
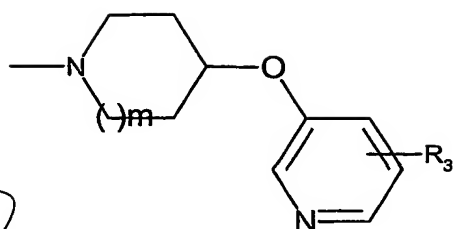
q is 1 or 2;

Q is -O- or -NH-;

and R<sub>q</sub> is R<sub>c</sub> which is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent); or a physiologically-tolerable salt thereof.

3. A compound according to either claim 1 or claim 2 wherein q is 2.

4. A compound according to any of claims 1 to 3 wherein -Lp(D)<sub>n</sub> is selected from the following formulae:



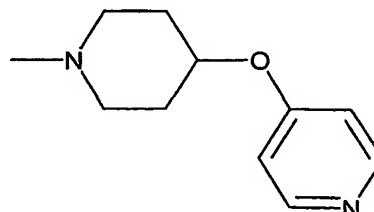
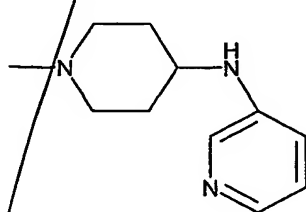
5

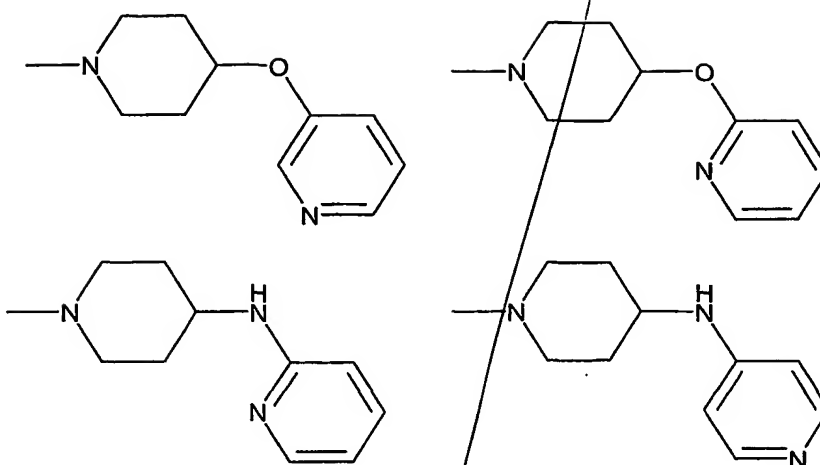
wherein:

m represents 0 or 1; and

when  $R_3$  is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxy carbonyl, acetyl amino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

- 15 5. A compound according to any of claims 1 to 3 wherein -Lp(D)n is selected from the following formulae:





6. A compound according to any one of claims 1 to 5 wherein  
5 Q is -NH-.

7. A compound according to any of claims 1 to 3 wherein R<sub>c</sub>  
is pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazin-3-yl,  
pyridazin-4-yl, pyrimid-4-yl or phenyl.

8. A compound according to any of claims 1 to 3 wherein R<sub>c</sub>  
is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-  
methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-  
methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

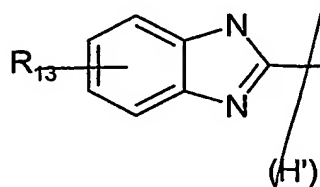
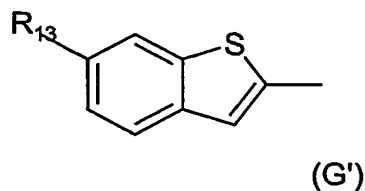
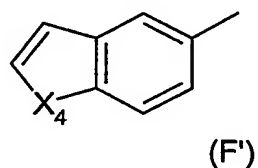
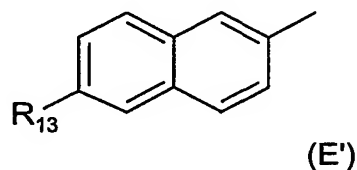
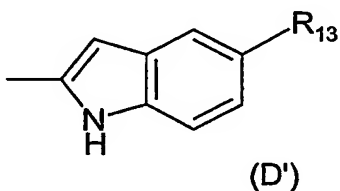
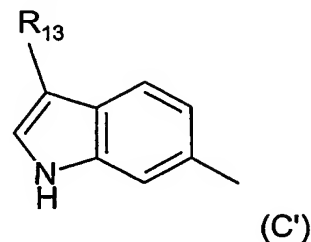
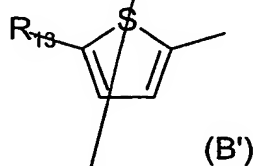
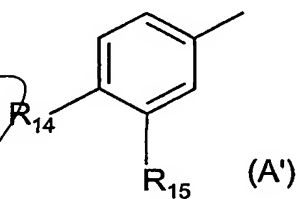
9. A compound according to any one of claims 1 to 8 wherein  
R<sub>2</sub> is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl,  
benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl  
(each of which is optionally substituted as defined in claim  
10 1).

10. A compound according to any one of claims 1 to 9 wherein  
optional substituents for R<sub>2</sub> are selected from:

fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy,  
trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano,  
trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino,

carboxy, acetoxy, hydroxy, methyl, ethyl, amido (CONH<sub>2</sub>), aminomethyl, methoxy and ethoxy.

11. A compound according to any one of claims 1 to 10 wherein R<sub>2</sub> is selected from one of the formula (A') to (H'):



wherein X<sub>4</sub> is O or S, R<sub>13</sub> is selected from hydrogen, chloro or methyl and R<sub>14</sub> is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R<sub>15</sub> is selected from hydrogen, methyl, fluoro, chloro and amino.

12. A compound according to claim 11, wherein R<sub>2</sub> is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

13. A compound according to any one of claims 1 to 12 wherein  
-X-X- is -CONH-.

5

14. A compound according to any one of claims 1 to 13  
wherein Y is CH.

15. A compound according to any one of claims 1 to 14  
10 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl,  
thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl,  
isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl,  
1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl,  
pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl  
15 or cycloalkyl group, or a phenyl group substituted by R<sub>3i</sub>X<sub>i</sub> in  
which X<sub>i</sub> is a bond, O, NH or CH<sub>2</sub> and R<sub>3i</sub> is phenyl or pyridyl  
optionally substituted by R<sub>3a</sub>.

16. A compound according to any one of claims 1 to 14,  
20 wherein Cy is an optionally R<sub>3a</sub> substituted: phenyl, pyridyl,  
thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

17. A compound according to any one of claims 1 to 16  
wherein R<sub>3a</sub> is selected from hydrogen, hydroxyl, alkoxy, alkyl  
25 (optionally substituted by hydroxy, alkylamino, alkoxy, oxo,  
aryl or cycloalkyl), aminoalkyl (optionally substituted by  
hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl),  
hydroxyalkyl (optionally substituted by hydroxy, alkylamino,  
alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl,  
30 alkylaminocarbonyl, alkoxycarbonylamino, alkylamino  
(optionally substituted by hydroxy, alkylamino, alkoxy, oxo,  
aryl or cycloalkyl), amino, halo, cyano, nitro, thiol,  
alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido,  
alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a



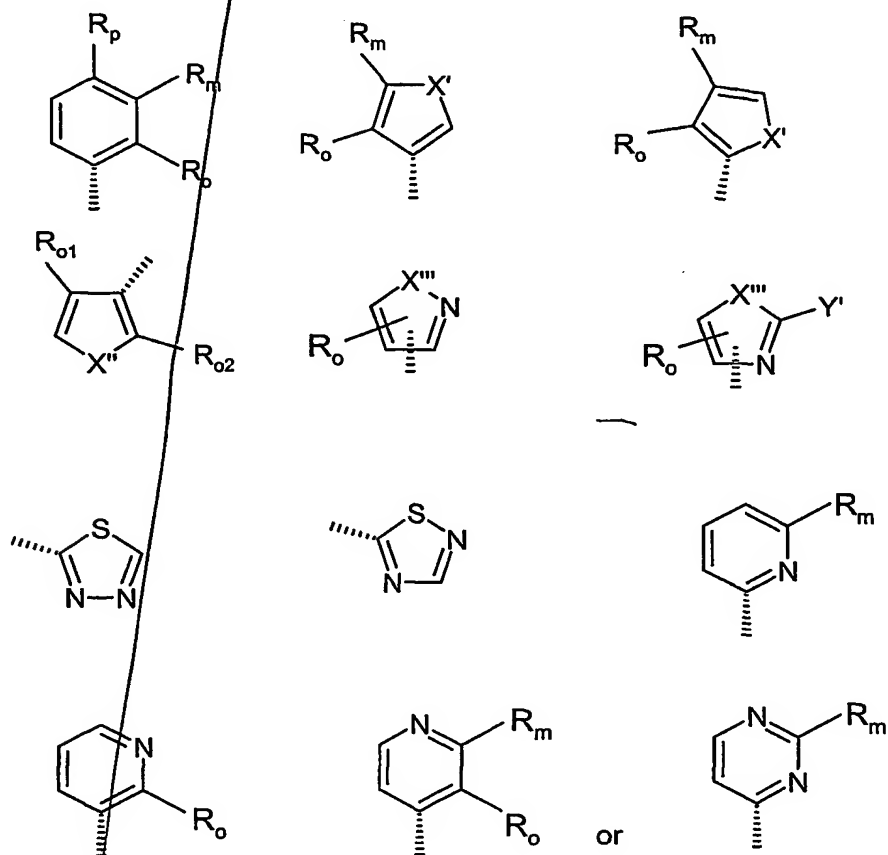
group of the formula  $-C(X^3)N(R^{11})R^{12}$  (wherein  $X^3$  is O or S; and  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and  $-OCH_2O-$  which is bonded to two adjacent ring atoms in Cy.

18. A compound according to any one of claims 1 to 16 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

20

19. A compound according to any one of claims 1 to 16 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,  $CONH_2$ ,  $CH_2CONH_2$ , acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and  $-OCH_2O-$  (which is bonded to two adjacent ring atoms in Cy).

20. A compound according to any one of claims 1 to 16 wherein  $R_{3a}$  is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl,  $CONH_2$ ,  $CH_2CONH_2$ , acetyl amino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.
21. A compound according to any one of claims 1 to 16 wherein Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

5 X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R<sub>O</sub> is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

10 R<sub>m</sub> is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula -C(X<sup>3</sup>)N(R<sup>11</sup>)R<sup>12</sup> (wherein X<sup>3</sup> is O or S, and R<sup>11</sup> and R<sup>12</sup> are independently selected from hydrogen, methyl or ethyl or  
15 together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);  
R<sub>p</sub> is selected from hydrogen and fluoro; or  
R<sub>O</sub> and R<sub>m</sub> or R<sub>m</sub> and R<sub>p</sub> form an -OCH<sub>2</sub>O- group; or  
R<sub>O</sub> and R<sub>m</sub> together with the ring to which they are attached  
20 form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and  
one of R<sub>O1</sub> and R<sub>O2</sub> is hydrogen and the other is R<sub>O</sub>.

25 22. A compound according to any one of claims 1 to 16 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-  
30 yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinclin-4-yl, quinolin-5-yl and quinolin-8-yl.

23. A compound as claimed in Claim 1, which is selected from 1-(indol-6-carbonyl-D-phenylglyciny)-4-(4-pyridoxy)-

piperidine; 1-[indole-6-carbonyl-D,L-(2-chlorophenyl)glyciny]-4-(pyridin-4-yloxy)piperidine, and physiologically-tolerable salts thereof.

24. A compound as claimed in any one of Claims 1 to 23, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D- $\alpha$ -aminoacid  $\text{NH}_2\text{-CR}_{1b}(\text{Cy})\text{-COOH}$  where the  $\text{NH}_2$  represents part of X-X.

25. A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 24 together with at least one pharmaceutically acceptable carrier or excipient.

26. A compound as claimed in any one of Claims 1 to 24 for use in therapy.

27. Use of a serine protease inhibitor according to any one of Claims 1 to 24 for the manufacture of a medicament for the treatment of a thrombotic disorder.

28. A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 24 together with at least one pharmaceutically acceptable carrier or excipient for use in the treatment of a thrombotic disorder.

29. A method of treatment of the human or non-human animal body to combat a thrombotic disorder, said method comprising administering to said body an effective amount of a compound according to Claim 1.

30. A compound of formula I as claimed in Claim 1 and named in any one of the Examples herein, or a physiologically acceptable salt thereof.